Boric Acid

CAS #10043-35-3
Swiss CD-1 mice, at 0.0, 1000, 4500, and 9000 ppm in feed
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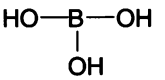

Boric acid (BA), widely used for both medicinal and nonmedicinal purposes, was known to adversely affect reproduction and fertility in rodents. NIOSH, in evaluating the literature prior to writing a Criteria Document, asked NIEHS to perform an RACB study on BA to generate both structural and functional data to be used for setting exposure criteria (Fail et al., Fundam Appl Toxicol 17:225–239 [1991]). Task 1, the dose range finding phase, was not conducted. Instead, dosages for the Task 2 continuous cohabitation phase were set at 0, 1000, 4500, and 9000 ppm in feed, based on sufficient data already existing in the literature. Using body weight and feed consumption data, the estimated average daily dose values were calculated to be approximately 145, 725, and 2150 mg/kg/day.

For the first generation, weight was reduced by approximately 15% in the high dose mice. Body weight reduction in the middle dose group was probably secondary to the fertility effect (see below). Clinical signs at the high dose included ocular effects (lacrimation, exopthalamos, cloudiness) and mild hair loss. Feed consumption was generally increased for middle and high dose animals (10–20%), as was water consumption.

BA produced significant reproductive toxicity. The high dose group was sterile from the beginning of cohabitation; no litters were ever delivered. At 4500 ppm, average litters per pair dropped by 51% and live pups per litter dropped by 36%, while adjusted live pup weight dropped by 14%. Cumulative days to the third litter was increased by 44% with a small sample size (6). Only one pair at 4500 ppm delivered a fourth or fifth litter. There were no effects on fertility noted at 1000 ppm.

The last litter from Task 2 was reared by the dam until weaning. All pups born at 4500 ppm died prior to weaning (n=4), and no litters were ever delivered at 9000 ppm. Thus, controls and 1000-ppm animals were evaluated, and there was no difference between these two groups in terms of body weights or viability to weaning.

After the last litter was reared and weaned, F_0 mice from the control and 4500-ppm groups were used for the Task 3 crossover mating trial. Whereas 14 of 19 control and 13 of 20 BA-treated females delivered a litter, only 1 of 20 pairs with a treated male delivered a litter. That litter contained 3 pups, compared to 11 control and 10 pups in litters from a treated dam. However, the adjusted pup weight in litters from BA-exposed dams was reduced by approximately 9%. Thus, though both sexes showed an effect, the larger effect was seen with BA-treated males.

After delivery of the Task 3 litters, all F_0 mice were killed and necropsied. While controls and 4500-ppm mice were given a "full" necropsy, the 1000- and 9000-ppm mice received a limited necropsy, focusing on body weight and the reproductive organs. Male body weight at 9000 ppm was reduced by approximately 15%. Absolute testes weight was reduced by 51 and 86% at 4500 ppm and 9000 ppm, respectively. Interestingly, although adjusted cauda epididymis weight was unchanged, the weight of the rest of the right epididymis (adjusted for body weight) was reduced by approximately 18 and 23% in the middle and high dose groups, respectively. Sperm parameters were severely affected: at the high dose, sperm count was reduced to 0.5% of the control value. In the middle dose, count and percent motile were reduced by 72 and 32%, while morphologic abnormalities were increased by 53%. In the low dose, the only change was a 12% reduction in motility. The only histologic abnormalities were seen in testes and epididymis (atrophy, aspermia); no renal or hepatic lesions were seen.

In females, adjusted liver weight and kidney weight were reduced by 6 and 5%, respectively. No changes occurred in estrous cycle length. Again, no ovarian, renal, or hepatic lesions were seen microscopically.

Task 4, the F_2 generation assessment, was conducted using the last litter from Task 2. Again, only low dose offspring were used since no litters were available from middle or high dose groups. In this mating trial, numbers and viability of the F_2 pups were not altered, even though the adjusted live pup weight dropped very slightly (3%).

The F_1 adults were killed and necropsied after the F_2 litters were evaluated. There were no differences between the control and the 1000-ppm males or females for any organ weight or for sperm parameters, although estrous cycle length was reduced for treated females from 4.7 to 4.2 days. Treated females also spent more time than the controls in diestrous. Histologically, there was no difference between the treated and control mice.

In conclusion, this study shows that boric acid in mice is a potent reproductive toxicant in males and females, as shown by the data from the Task 3 crossover mating (male sterility and sperm effects) and from the reduced pup weight (Tasks 3 and 4) and changed estrous cycle (Task 4).

Summary: NTP Reproductive Assessment by Continuous Breeding Study.

NTIS#: **PB90253808**
Chemical: **Boric Acid**
CAS#: **10043-35-3**
Mode of exposure: **Feed**
Species/strain: **Swiss CD-1 mice**

F_0 generation — Dose concentration →	1000 ppm	4500 ppm	9000 ppm
General toxicity	Male, female	Male, female	Male, female
Body weight	—, •	—, —	↓, •
Kidney weight[a]	•, •	—, ↓	•, •
Liver weight[a]	•, •	—, ↓	•, •
Mortality	—, —	—, —	—, —
Feed consumption	—, —	↑, ↓	↑, ↓
Water consumption	—, —	↑, ↓	↑, ↓
Clinical signs	—, —	—, —	↑, —
Reproductive toxicity			
x̄ litters/pair	—	↓	ID
# live pups/litter; pup wt./litter	—, —	↓, ↓	ID
Cumulative days to litter	—	↑	ID
Absolute testis, epididymis weight[a]	—, —	↓, —	↓, —
Sex accessory gland weight[a] (prostate, seminal vesicle)	•, •	—, —	•, •
Epidid. sperm parameters (#, motility, morphology)	—, ↓, —	↓, ↓, ↑	↓, -(ss), -(ss)
Estrous cycle length	—	—	—

Determination of affected sex (crossover)	Male	Female	Both
Dose level	4500 ppm	—	—

F_1 generation — Dose concentration →	1000 ppm	4500 ppm	9000 ppm
General toxicity	Male, female	Male, female	Male, female
Pup growth to weaning	—, —	-(ss), -(ss)	ID
Mortality	—, —	-(ss), -(ss)	ID
Adult body weight	—, —	•, •	•, •
Kidney weight[a]	—, —	•, •	•, •
Liver weight[a]	—, —	•, •	•, •
Feed consumption	—, —	•, •	•, •
Water consumption	—, —	•, •	•, •
Clinical signs	—, —	•, •	•, •
Reproductive toxicity			
Fertility index	—	•	•
# live pups/litter; pup wt./litter	—, ↓	•, •	•, •
Absolute testis, epididymis weight[a]	—, —	•, •	•, •
Sex accessory gland weight[a] (prostate, seminal vesicle)	—, —	•, •	•, •
Epidid. sperm parameters (#, motility, morphology)	—, —, —	•, •	•, •
Estrous cycle length	↓	•, •	•, •

Summary information	
Affected sex?	Both
Study confounders:	No offspring at 9000 ppm
NOAEL reproductive toxicity:	<1000 ppm
NOAEL general toxicity:	1000 ppm
F_1 more sensitive than F_0?	No
Postnatal toxicity:	Unknown

Legend: —, no change; •, no observation; ↑ or ↓, statistically significant change ($p<0.05$); — , —, no change in males or females; ss, small sample size; ID, insufficient data. [a]Adjusted for body weight.